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Pathophysiology of Complication in Diabetes Mellitus

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Blood sugar levels are elevated in diabetes mellitus (DM), the most prevalent metabolic disorder. Insulin deficiency or ineffectiveness is the primary cause of hyperglycemia, affecting carbs and protein, and fat metabolism. Diabetes mellitus can be of two types, type 1 and type 2. Apart from this, a certain amount of people suffers from prediabetes. Type 1 diabetes insulin-dependent dent diabetes happens when the pancreas produces less or no insulin, so these patients require insulin doses frequently. A patient has type 2 diabetes if the cells don't respond to insulin. This is the most common kind of diabetes and affects 95% of people with diabetes. It is an insulin-independent type of diabetes. Nearly every organ in the body is affected by DM. Microvascular and macrovascular problems are caused by diabetes mellitus. Nephropathy (disease of the kidney), retinopathy (eye damage), and neuropathy (nerve damage) are examples of microvascular complications, whereas macrovascular complications include blood vessels, arteries, and veins, e.g., peripheral artery disease, cerebrovascular events, etc. Retinopathy is a visual manifestation of end-organ damage. Neuropathy is of two types: symmetrical and asymmetrical. Symmetrical neuropathy is primarily sensory and autonomic, whereas asymmetrical neuropathy may be sensory, motor, or both. Diabetes is a long-term medical condition, and no medications are available to treat the secondary issues in today's market; it cannot be cured but may be controlled by a healthy lifestyle. Continuous, frequent glucose hemostasis is critical.

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1. INTRODUCTION

An abnormality in insulin synthesis or insulin activity, or both, results in chronic hyperglycemia in diabetes mellitus. Diabetic individuals usually have compromised exocrine pancreas function [1]. As an anabolic hormone, insulin disrupts the metabolism of carbohydrates, lipids, and proteins. As the condition progresses and worsens, it has an increasing impact on the organ systems throughout the body [2]. As insulin receptors, signal transduction mechanisms, and effector enzymes or genes are implicated, metabolic diseases are caused by low insulin levels, particularly in skeletal muscles, adipose tissue, and the liver. When your cells cannot use glucose (glucose) as a source of energy, diabetes develops. As a consequence, your body gets flooded with sugar [3]. For both people and society as a whole, the long-term impacts of diabetes may have catastrophic repercussions [4]. Haemoglobin HbA (1C) has been clinically utilized to evaluate diabetics' glycemic control [5].

2. EPIDEMIOLOGY

People with diabetes in India have been diagnosed at a rate of 62 million per year. The number of individuals affected by diabetes is ever-increasing [6]. Approximately 31.7 million individuals in India, China, and the USA were diagnosed with diabetes mellitus in 2000. (17.7 million). It is predicted that the number of patients who have diabetes are will rise from 171 million in 2000 to 366 million by 2030, and India is said to expect the most significant increase. Up to 79.4 million people in India are anticipated to be affected by diabetes by 2030. The term "pre-diabetes" refers to elevated blood sugar levels that don't match the criteria for a diabetes diagnosis. In the United States, it affects 54 million people. The chance of acquiring type 2 diabetes is more significant in patients with prediabetes [7].

3. DIAGNOSIS [3]

The range of glucose levels is often kept relatively tight, generally between 70 mg/dL and 120 mg/dL. Diagnosis of diabetes is made up of the following components:

Equilibrium is defined as a blood sugar level below 100 mg/dL, or less than 140 mg/dL, after an oral glucose tolerance test (OGTT). Individuals with impaired glucose tolerance, often called “pre-diabetics,” have fasting glucose readings more than 100 mg/dL but less than 126 mg/dL, or OGTT levels greater than 140 mg/dL but less than 200 mg/dL. Pre-diabetic people have a substantial chance of developing diabetes mellitus, with up to 5% to 10% developing the disease over time. The aberrant glucose metabolism of pre-diabetics and the combination of additional risk factors, such as low HDL, hypertriglyceridemia, and elevated plasminogen activator inhibitor-1, raises the possibility of developing heart diseases in these individuals (PAI-1)

Table 1. Classification of diabetes mellitus [3]

1. Type 1 diabetes (Destruction of β-cell, which may lead to absolute insulin deficiency) Immune-mediated Idiopathic
2. Type 2 diabetes presence of both insulin resistance and β-cell dysfunction)
3. Genetic defects of β-cell function
4. Genetic defects in insulin action
- Type A insulin resistance
-Lipoatrophic diabetes, including mutations in PPARG
5. pancreatic endocrinopathy
-Surgical removal of the pancreas
-Tumour
-Mucoviscidosis
-Chronic pancreatitis
-Hemochromatosis
-Fibrocalculous pancreatopathy

6. Endocrinopathies
-Acromegaly
-hypercortisolism
-Hyperthyreosis
-Paraganglioma
-Glucagon secreting pancreatic neuroendocrine tumor
7. Infections
-Coxsackie B virus
- Cytomegalovirus
-Congenital rubella
8. Drugs
-Corticosteroids
-Thyroid hormone
9. **Genetic syndromes associated with diabetes**
-Down's syndrome
-47, XXY syndrome
-Ullrich-Turner syndrome
-Prader-Willi syndrome
10. Gestational diabetes mellitus

4. PATHOPHYSIOLOGY OF DIABETES MELLITUS

4.1 Type 1DM

Up to 79.4 million people in India are anticipated to be affected by diabetes by 20302. The term "pre-diabetes" refers to elevated blood sugar levels that don't match the criteria for a diabetes diagnosis. In the United States, it affects 54 million people. There is a greater chance of acquiring type 2 diabetes in those already suffering from pre-diabetes [7]. Insulin must be given to those with Type 1 diabetes every day. Hence the name "insulin-dependent diabetes." There are three distinct symptoms of type 1 diabetes: Polyuria, Polydipsia, and Polyphagia [7]. CD4+ and CD8+ T lymphocytes induce type 1 diabetes, which results in insulin deficiency, glucagon overproduction, and pancreatic beta cells are unable to respond to all insulin secretory stimuli. More than 95 percent of persons with type 1 diabetes have HLA-DR3 or HLA-DR4 in their blood. HLA-DQs are classified as adaptive immunity class II peptide markers for type 1 DM susceptibility, meaning that they represent a specialized marker for this form of immunity. Genes and environmental factors have a role in producing autoantibodies against numerous islet cell components, such as GAD-65 antibodies, ICA512/IA-2 antibodies, insulin antibodies, and insulin-like peptide antibodies (ILP) (IAA). Diabetic dyslipidemia, which is characterized by low High-density lipoprotein and high TG-rich particles (such as VLDL and chylomicrons), may result in a large number of ketone bodies in the body such as acetoacetate, acetone, and -hydroxybutyrate, which can lead to coma in patients who have type 1 diabetes. Amino acids are targeted and converted to glucose by gluconeogenesis due to a shortage of intracellular glucose, resulting in loss of muscle mass. Hyperglycemic coma is caused by hyperosmotic plasma created by hyperglycemia outside the body. Dehydration and a loss of consciousness in an older person are typical symptoms of the condition, characterized by hyperglycemia but no signs of ketoacidosis. The initial sign of elevated blood glucose levels is in the urine, followed by various additional symptoms [8].

4.2 Type 2 DM

This form of diabetes happens when your body doesn't create sufficient insulin or your cells don't respond to insulin appropriately. The most frequent kind of diabetes is Type 1 Type 2 diabetes, affecting about 95% of people with diabetes. Middle-aged and older adults are more susceptible to this condition.

Type 2 DM patients have a higher susceptibility to short-term and long-term issues [9].

Although Type 2 diabetes has traditionally been seen in both young and older adults, it is seen more prominently in children as a result of an increase in infant weight problems and inactivity; the cause is oxidative stress, downregulation of insulin receptors within peripheral tissue, and a discount within the range of insulin receptors; this is due to an increase in infant weight problems and inactivity; insulin resistance causes a

compensatory hyperinsulinemic state because of the inadequate response of the insulin system. Cardiovascular diseases (CVD) such as coronary heart attack, stroke, hypertension, and a variety of other issues, such as deadly non-alcoholic fatty liver disease (NAFLD), polycystic ovary disorder (PCOD), hepatocarcinoma, bowel cancer, breast carcinoma, prostatic adenocarcinoma, impaired cognitive characteristics, etc., are all associated with syndrome X.

Additionally, anomalies of the mobile glucose receptor, which reacts to substantially greater glucose attention or relative molecular shortfall, as well as excess hyperglycemic hormones, are other causes of type 2 diabetes.

Histological alterations in the pancreas occur in both types of diabetes, type 1 and type 2 [10].

5. A SUMMARY OF DIABETES COMPLICATIONS [4]

Autonomic neuropathy • Peripheral neuropathy • Central nervous system stroke (Motor & sensory dysfunctions)

• Cataracts • Retinopathy • Blindness

Myocardial infarction, atherosclerosis, hypertension, and malfunction of endothelial cells all affect the cardiovascular system.

Mouth • Mouth illness (Caries, gingivitis, periodontal abnormalities, infections)

In addition to nephropathy, proteinuria, glucosuria, and kidney failure.

• Diarrhea • Constipation • Dyspepsia • Exocrine gland insufficiency • Delayed gastric emptying

Impotence, sexual dysfunction, and urogenital dysfunction all fall under this category.

• Impaired wound healing • Infection of the skin

Fractures, osteoporosis, and osteopenia

Amputation of the foot is the most common cause of foot ulceration.

6. MICROVASCULAR COMPLICATIONS

Retinopathy In type 1 and type 2 diabetes mellitus, diabetic retinopathy (DR) is an established consequence found in virtually all type 1 and 75% of type 2 diabetics after 15 years of diabetes. Diabetic retinopathy is a visual manifestation of end-organ damage [11]. Proliferative diabetic retinopathy (PDR) and nonproliferative diabetic retinopathy (NPDR) are the two major types of DR (PDR). Early indications include microaneurysms and retinal hemorrhages, which are the first indicators of NPDR. Cotton-wool patches, venous beading, and intraregional microvascular anomalies are all signs of capillary nonperfusion. With increased retinal ischemia, alternate vascular pathways form on the retina and the vitreous's posterior surface. Diabetic macular edema (DME) affects only 3% of cases with mild NPDR, whereas 40% of cases with moderate to severe NPDR develop DME. DME occurs in 71% of people with diabetes who also have proliferative diabetic retinopathy (PDR). Diabetic macular edema and PDR contribute to diabetic retinopathy's visual impairment. In people with diabetes with poor blood sugar management, high blood pressure, high cholesterol, pregnancy, smoking, etc., the likelihood of progressing to retinopathy is higher.

6.1 Nephropathy

To identify microalbuminuria, a random spot sample of urine should be taken, and the albumin-to-creatine ratio should be determined. Microalbuminuria linked with diabetic kidney disease was assessed at 30-299 mg/24 hours in a 24-hour urine collection, 20-199 g/min in timed urine collection, or 30-299 g/mg creatinine in a spot urine collection on the day of the study; at least two times during three months. Microalbuminuria is more commonly seen in individuals with type 2 DM than those with 1 DM. Microalbuminuria has an abnormal value of 150-300 mg/day, and macroalbuminuria has more than 300 mg/day. However, it has been proved that the possibility of getting diabetes-related nephropathy and cardiovascular disease might be there even if the urine albumin removal levels are within normal ranges for albumin excretion in diabetic patients. Glycosylated hemoglobin, or HbA1C, has been linked to the development of nephropathy in type 1 diabetes. All progressive renal disorders are adversely affected by hypertension, but diabetic glomerulosclerosis, characterized by thickening the glomerular cellar layer and enlargement of the lacis cells with increased extracellular matrix deposition, seems to be particularly so [12].

6.2 Neuropathy

Worldwide, diabetes is the most probable cause of neuropathy. Patients with symptoms and

indications of neuropathy with diabetes who have had alternative explanations ruled out are called diabetic neuropathy [11]. Diabetic neuropathies are divided into symmetrical and asymmetrical (focal or multi-focal). Symmetrical neuropathies are predominantly sensory and autonomic, whereas asymmetrical neuropathies may be sensory, motor, or both. In this context, neuropathy that affects the longest nerve first before spreading proximally is known as diabetic peripheral neuropathy or stocking-glove neuropathy. The most common and leading cause of lower limb amputation is in diabetic patients with distal symmetrical peripheral neuropathy, also known as diabetic sensory-motor peripheral neuropathy.

Consequently, neuropathy must be monitored and its severity level determined to devise the optimal treatment strategy. An NDS of at least six is required for a person to be diagnosed with severe neuropathy.

6.3 Macrovascular Complications

A study of the diabetic community found that more than three out of every four diabetics died from atherosclerosis-related causes and, in most instances (75 percent) from Ischemic heart disease. Type 2 diabetes is associated with an increased risk of ischemic heart disease (CAD) by 2-4 times in the general population. Plaques are formed due to atherosclerosis, which is charactecharacterizedildup by fatty deposits. Acute coronary syndrome (ACS) is a medical emergency that results from the rapid rupture of a coronary artery plaque. Even while ACS, unstable angina and acute myocardial infarction may all be diagnosed using measurements of cardiac enzymes and markers, ECG changes or increases in biochemical markers are the primary tools for diagnosis of all three conditions. Cardiac indicators such as troponin T and troponin I may be tested. A concept of acute coronary syndromes and myocardial infarctions is given.

6.4 Peripheral Arterial Disease (PAD)

Atherosclerosis is the primary cause of PVD, Peripheral artery disease, also known as a peripheral vascular disease (PVD), affects the big peripheral arteries (particularly those in the legs). ABPI measurement has been established as the go-to non-invasive, low-cost test for diagnosing plantar fasciitis. Additionally, patients with an abnormal blood pressure index (ABPI) less than 0.90 are diagnosed with peripheral artery disease (PAD) even if they have no symptoms. Hemodynamically, this suggests an obstruction in the artery. Risk factors for peripheral vascular disease (PVD) include age, obesity, smoking, diabetes, and hypertension, and nontraditional risk factors such as religion, race, chronic renal disease, and hypercoagulable states.

Table 2. Stage wise history of PAD

Stage	History
1	No symptoms
2a	Mild Cramps
2b	Moderate to Severe Cramps
3	Ischaemic Rest Pain
4	Tissue Loss or Ulcers

Rest discomfort and ulceration are both signs of critical limb ischemia and may be detected by calculating the arterial blood pressure index (ABPI), which is normal when it is more than or equal to 1, but suggests mild to moderate leg pain or ulceration when it is between 0,5 and 0,9.

6.5 Cerebrovascular Events (CVA)

People with diabetes are thrice more likely to get a stroke or a transient ischemic attack (TIA), both of which are cerebrovascular disorders. In addition, people with diabetes are more likely to die from a stroke and suffer from more severe disabilities than their nondiabetic counterparts [3,5]. Cerebral small vessel disease and atherosclerosis of the cervical and intracranial arteries are the two most common causes of CVA in diabetic people. Blood flow to the brain is disrupted by cerebral vascular disease, which causes TIAs and strokes. Blockage of the blood arteries that supply the brain may cause dizziness, disorientation, blindness, double vision, difficulties speaking, and an intense headache if the blood pressure in the brain rises over 140/90 mmHg [6,3]. In a new study, researchers found that diabetes influences the sort of stroke a person suffers. Subcortical fits or infarcts are more frequent in diabetes than non-diabetics, and ischemic stroke is more common than hemorrhagic stroke [13-19].

7. CONCLUSION

Insulin production or action, or both, maybe impaired in people with diabetes, which is a long-term medical condition. The buildup of glucose in the bloodstream is the most significant diabetes mellitus. There are no medications available to

treat these secondary issues in today's market. Diabetic Mellitus (DM) cannot be cured, but it may be controlled by proper eating, exercise, and medication. If one wants to reduce the long-term complications of diabetes, continuous, frequent glucose homeostasis is critical. Preventing the onset and reducing the progression of both macrovascular and microvascular problems of diabetes may be achieved by better control of blood sugar levels. A score of 0.4 indicates critical limb ischemia (pain/ulceration).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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